# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP2005/000741 | 26.01.2005 | 29.01.2004 |

International Patent Classification (IPC) or both national classification and IPC
A61K38/04, A23L1/305, A61P25/00

Applicant
EBEWE PHARMA GES.M.B.H. NFG. KG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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ATTACHMENT D

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000741
10/587859

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-15 ( with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 9-15 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

## Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

## Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-15 relating to inv.2 |
| | No: | Claims | 1-15 relating to inv.1 |
| Inventive step (IS) | Yes: | Claims | 1-15 relating to inv.2 |
| | No: | Claims | 1-15 relating to inv.1 |
| Industrial applicability (IA) | Yes: | Claims | 1-8 relating to inv.1 and 2 |
| | No: | Claims | - |

2. Citations and explanations

**see separate sheet**

## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III.**

Claims 9-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV.**

The separate inventions are:

Invention 1: claims 1-15 (all partially)
Dietary supplement mixture comprising at least the peptide defined by Sequence 1: NMVPFPR, oral dosage forms comprising said mixture and uses of said mixture for preventing or ameliorating age-associated cognitive decline or age-associated neuronal dysfunctions.

Invention 2: claims 1-15 (all partially)
Dietary supplement mixture comprising at least the peptide defined by Sequence 2: ASAFQGIGSTHWVYDGVGNS, oral dosage forms comprising said mixture and uses of said mixture for preventing or ameliorating age-associated cognitive decline or age-associated neuronal dysfunctions.

The application lacks unity of inventions as required by Article 3(4)(iii) and 17(3)(a) PCT for the following reason:

The inventions as defined above relate to dietary supplement mixtures comprising two different peptides.

The common concept underlying the present application is that those peptide-containing dietary supplement mixtures prevent or ameliorate age-associated cognitive decline or age-associated neuronal dysfunction.

A dietary supplement mixture, which contains a peptide and which prevents or ameliorates age-associated cognitive decline or age-associated neuronal dysfunction is already known in the art (please see EP1188767, claim 6, paragraph [0021], [0091]).

In light of this prior art the above mentioned common concept is not novel and the problem underlying the present application can be redefined as:

The provision of additional dietary supplement mixtures.

The dietary supplement mixtures identified in inventions 1 and 2 are different solutions to this problem.

Due to the fact that a dietary supplement mixture, which contains a peptide and which prevents or ameliorates age-associated cognitive decline or age-associated neuronal dysfunction is known in the prior art and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT due to the essential differences in the primary structures of the peptides contained in these mixtures, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT.

Consequently, the application lacks unity of invention and the different inventions are as formulated above.

**Re Item V.**
**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Novelty and inventive step (Art. 33(2)(3), PCT) of invention 1**

Reference is made to the following document:

D1: WO 02/46767 A (OXFORD GLYCOSCIENCES LTD) 13 June 2002 (2002-06-13)

**1.1** It is pointed out that the present communication only refers to subject-matter which does not fall under the provision of Rule 67.1(iv) PCT (see Item III).

**1.2** The present invention 1 refers to a composition comprising a peptide with the amino acid sequence 1 (NMVPFPR), medical compositions for oral application comprising said peptide and the use of said composition as a dietary supplement for preventing or ameliorating age-associated cognitive decline or age-associated neuronal dysfunctions.

**1.3** D1 discloses many peptides and polypeptides and their use in the treatment of Alzheimer's disease, which is described as an age-associated neurodegenerative disease (page 1, lines 12-14). The peptide defined by SEQ ID NO:393 consists of 10 amino acids, which are 100% identical in position 4-10 to the sequence of the claimed peptide. Further, D1 not just claims a peptide of SEQ ID NO:393 but also **fragments of said peptide** for the prevention and treatment of Alzheimer's disease as a specific age-associated neurodegenerative disease (page 160, line 5-page 162, line 7). The specific sequence of the claimed peptide is however not mentioned. As long as no **specific effect** of the claimed peptide, which is **unexpected in view of the teaching of D1** has been credibly demonstrated, subject-matter of present claims 1-15 is not novel and not inventive according to Art. 33(2)(3), PCT.

**1.4** For the assessment of the present claims 9-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## 2. Novelty and inventive step (Art. 33(2)(3), PCT) of invention 2

Reference is made to the following documents:

D2: SAUTTER A ET AL: "An isoform of the rod photoreceptor cyclic nucleotide-gated channel beta subunit expressed in olfactory neurons" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, no. 8, 14 April 1998 (1998-04-14), pages 4696-4701, XP002285826 ISSN: 0027-8424

D3: WO 01/75067 A (HYSEQ, INC.) 11 October 2001 (2001-10-11)

**2.1** It is pointed out that the present communication only refers to subject-matter which does not fall under the provision of Rule 67.1(iv) PCT (see Item III).

**2.2** Present invention 2 refers to a composition comprising a peptide with the amino acid sequence 2 (ASAFQGIGSTHWVYDGVGNS), medical compositions for oral application comprising said peptide and the use of said composition as a dietary supplement for preventing or ameliorating age-associated cognitive decline or age-associated neuronal dysfunctions.

**2.3** Document D2 discloses the protein sequence of rat CNG4.3 (cyclic nucleotide-gated channel) subunit, which overlaps from amino acids 427-446 with the peptide of SEQ ID NO:2. A medical application of a fragment of CNG4.3 or its use in dietary supplements is not disclosed.

**2.4** Document D3 claims a large number of human proteins and mentions the use of said proteins i.a. for treating Alzheimer's disease (p.45, l.19-30; p. 59, l. 1-p. 60, l. 29). The protein defined in SEQ ID NO:57830 displays a sequence identity of 90% in residues 213-232 with the peptide of SEQ ID NO:2 of the present application. Neither modifications of the protein SEQ ID NO:57830 nor specific fragments of said protein nor their use against Alzheimer's disease are mentioned.

**2.5** Since non of the cited documents refers to the exact peptide defined in SEQ ID NO:2, subject-matter of present claims 1-15 of invention 2 is novel according to Art. 33(2),

PCT.
Further, none of the cited documents alone or in combination would suggest to the skilled person that the exact peptide defined in SEQ ID NO:2 might be useful for preventing or ameliorating age-associated cognitive decline or age-associated neuronal dysfunctions. The subject-matter of present claims 1-15 of invention 2 is therefore not obvious and fulfils the requirement of Art. 33(3), PCT.

2.6 For the assessment of the present claims 9-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII.**

**3. Further remarks relating to inventions 1 and 2**

3.1 Upon entry into the regional phase at the EPO, claims directed to the medical use of a compound for which a therapeutic effect is already know in the art, will have to be phrased as so-called "2nd medical use claims" (e.g. use of X for the manufacture of a medicament for treating disease Y). In this respect, it is pointed out that the claim wording should refer to concrete diseases and/or disorders, but not to general mechanisms like "preserving /supporting healthy mental function during the aging process" (see claim 15). In this context it is reminded that the process of aging itself is not a disease or disorder.

3.2 The experiments as detailed in the present application all refer to a "mixture of the invention", which, according to example 1 and 4, contain "peptide". It is therefore not clear to which of the two peptides (SEQ ID NO:1 or 2) the experimental data refer to.